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Differential associations between depressive symptoms and glycaemic control in outpatients with diabetes

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Abstract

Aims Depression is common in people with diabetes, and related to higher HbA_{1c} levels. Depression, however, is a heterogeneous construct that involves a variety of symptoms. As little is known about the associations of individual depressive symptoms with HbA_{1c}, we explored these associations in outpatients with diabetes.

Methods The study was conducted in three tertiary diabetes clinics in the Netherlands. At baseline, the presence of the nine depressive symptoms that are listed in the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition was assessed with the nine-item Patient Health Questionnaire (PHQ-9). At baseline and after a 1-year follow-up, HbA_{1c} was derived from the medical charts.

Results A total of 288 out of 646 subjects with diabetes (45%) reported one or more depressive symptom(s). Depressed mood ($\beta = 0.11$, $P = 0.005$), sleeping difficulties ($\beta = 0.16$, $P < 0.001$), appetite problems ($\beta = 0.15$, $P < 0.001$) and suicidal ideation ($\beta = 0.14$, $P = 0.001$) were significantly related to higher baseline HbA_{1c} values. Furthermore, depressed mood ($\beta = 0.09$, $P = 0.03$) sleeping difficulties ($\beta = 0.12$, $P = 0.004$), appetite problems ($\beta = 0.11$, $P = 0.01$) and psychomotor agitation/retardation ($\beta = 0.09$, $P = 0.04$) were significantly related to higher HbA_{1c} values at 1-year follow-up. Associations were more pronounced in Type 1 diabetes than in Type 2 diabetes. None of the depressive symptoms were related to change in HbA_{1c} over time, except suicidal ideation.

Conclusion In people with diabetes, several individual depressive symptoms were related to higher HbA_{1c} levels. These associations persisted over time. More research is needed to investigate potential mechanistic pathways.

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Introduction

Depression is common in people with diabetes. A meta-analysis showed that the odds of depression are almost doubled in people with Type 2 diabetes compared with controls [1]. Although a systematic review concluded that data for Type 1 diabetes were insufficient to draw firm conclusions [2], a more recent study showed that the prevalence of depression was higher in Type 1 diabetes than in controls [3]. Depression is related to adverse outcomes in people with diabetes, including an increased risk for diabetes complications and mortality [4,5]. Poor glycaemic control might play a central, mediating role in these associations. A meta-analysis, published in 2000, showed that depression is related to higher HbA_{1c} levels, with standardized effect sizes in the small to medium range [6], and other studies have shown that elevated levels of HbA_{1c} are related to the development of diabetes complications and mortality [7–9].

Several longitudinal and intervention studies could not replicate an association between depression and HbA_{1c} [10–12]. The inconsistent findings regarding the relationship between depression and HbA_{1c} may be related to the heterogeneous concept and diagnosis of depression. The diagnosis of depression is based on the frequency and severity of a set of various symptoms. According to the Diagnostic and Statistical Manual, fourth edition (DSM-IV), a diagnosis of a major depressive disorder requires the presence of a minimum of five out of nine symptoms, including at least one of the two core symptoms of depression (depressed mood and diminished interest or pleasure in activities) to be present

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for at least 2 weeks. These symptoms should be accompanied by others, such as sleeping problems, alterations in movement and problems with concentration. Hence, persons with depression may substantially differ in the depressive symptoms they have. At present, little is known about the association of individual symptoms of depression with HbA_{1c}. Knowledge of the specific associations between individual depressive symptoms and HbA_{1c} may identify subsets of people with diabetes requiring specific therapeutic interventions. In addition, it may guide research on aetiology, as the various depressive symptoms might signify different pathophysiological pathways.

The aim of the study is to explore the association of individual symptoms of depression with HbA_{1c} in a large cohort of outpatients with diabetes. Previous studies indicated that high levels of HbA_{1c} are related to several indicators for poor sleeping quality in diabetes and fatigue [13,14]. We therefore hypothesized that a differential relationship exists between depressive symptoms and HbA_{1c}. We expected higher correlations for somatic depressive symptoms, such as fatigue and appetite problems, because these depressive symptoms reflect symptoms of prolonged hyperglycaemia.

Methods

Recruitment

This study was a secondary analysis of data from a multicentre depression screening research project in the Netherlands, which aimed to test whether screening for depression with subsequent feedback was related to a reduction in depressive symptoms compared with screening without feedback [15]. The study design has been described in more detail elsewhere [15,16].

Briefly, a random sample of 2055 outpatients with diabetes was drawn from patient registers of three tertiary diabetic clinics in the Netherlands: (1) 1000 outpatients of the VU University Medical Centre (Amsterdam), (2) 555 outpatients of the Haaglanden Medical Centre (The Hague) and (5) 500 outpatients of the Radboud University Medical Centre (Nijmegen). Patients were eligible for the current study if they were aged $\geq$ 18 years and had established diabetes (Type 1 or Type 2). Written consent was obtained from all participants, and the study was approved by the local medical ethics committee. The investigations were carried out in accordance with the principles of the Declaration of Helsinki.

Measurements

Participants received questionnaire booklets by mail in two phases. The first questionnaire booklet contained questions on socio-demographic and lifestyle characteristics. The second questionnaire booklet, which was sent to the participants after having received the first questionnaire, captured depressive symptoms. From the medical records of the patients, the following data were obtained: type of diabetes, duration of diabetes, treatment regimen, presence of microvascular complications, presence of cardiovascular disease, HbA_{1c} values and blood pressure.

Depressive symptoms

The presence and severity of depressive symptoms were assessed with the nine-item Patient Health Questionnaire (PHQ-9) [17]. This self-report questionnaire includes the nine symptoms of the DSM-IV criteria for a major depressive disorder, i.e. (I) lack of interest, (II) depressed mood, (III) sleeping difficulties, (IV) fatigue, (V) appetite problems, (VI) feelings of worthlessness, (VII) concentration problems, (VIII) psychomotor agitation/retardation and (IX) suicidal ideation. We assessed the presence of each symptom according to the scoring algorithm for the PHQ-9. Each symptom was scored as present if endorsed 'more than half the time' or 'nearly all the time'. Symptom 9 (suicidal ideation) was counted when the symptom was present at all. In addition, we classified our participants into those with and without elevated depressive symptoms using a PHQ-9 cut-off of $\geq$ 10 [17].

HbA_{1c}

The HbA_{1c} values were extracted from patients' medical records. Assessments were standardized and conducted within 3 months before completion of the PHQ-9. After 1 year, follow-up HbA_{1c} values were once more collected. Because HbA_{1c} was expressed in%, we used the mathematical formula ($10.93 \times HbA_{1c}$ value in% – 23.5) to recode the values in mmol/mol [18].

Statistical analysis

Only patients with complete data on depressive symptoms and baseline HbA_{1c} were included in the present analysis. Nine cross-sectional linear regression models were constructed for each individual depressive symptom to assess its association with HbA_{1c}. In a stepwise approach, we adjusted the nine linear regression models for the following potential confounders: sex, age, education level, ethnicity, insulin treatment, body mass index and smoking. We also studied whether the presence of elevated depressive symptoms (PHQ-9 score $\geq$ 10) was related to HbA_{1c} values in linear regression analysis. In sensitivity analyses, we stratified our analyses for type of diabetes. Furthermore, the linear regression analyses were repeated with (1) the 1-year follow-up values of HbA_{1c} and (2) change in HbA_{1c} from baseline to 1-year follow-up as outcomes. All analyses were conducted in SPSS Statistics, version 17.0. As this study was aimed at exploring associations, we made no adjustments for multiple testing [19]; P-values < 0.05 were considered as statistically significant.

Results

Of the 2055 invited patients with diabetes, 966 (47%) completed the first questionnaire, of whom 772 (80%) completed and returned the second questionnaire that captured depressive symptoms. A total of 646 participants had complete data on both HbA_{1c} values and PHQ–9. Table 1 shows the baseline characteristics of the total sample stratified by diabetes type. In our sample group 49% were female, the mean age was 53.3 (± 15.1) years, 57% had Type 2 diabetes and 91% were on insulin treatment (Type 1 diabetes: 100%, Type 2 diabetes 84%). Furthermore, 288 participants (45%) had one or more depressive symptoms present on the PHQ-9. Symptoms that were most often reported in the total sample were fatigue, sleeping difficulties, problems with concentration and appetite problems. Participants with Type 2 diabetes reported more sleeping difficulties, problems with concentration and appetite problems compared with participants with Type 1 diabetes.

Overall, mean baseline HbA_{1c} was 61 ± 14 mmol/mol (7.7 ± 1.3%). For 552 out of 646 participants (85%), 1-year follow-up HbA_{1c} levels were available and amounted 62 ± 14 mmol/mol (7.8% ± 1.3%). The Pearson correlation between HbA_{1c} values over time was high ($r = 0.78$, $P < 0.001$). The HbA_{1c} values did not differ for type of diabetes.

Figure 1 shows the mean baseline and follow-up values of HbA_{1c} for the presence and absence of each symptom of the PHQ-9. The presence of each symptom was related to higher HbA_{1c} levels, but the strength and statistical significance of the relationship varied over symptoms.

Cross-sectional analyses

Univariable linear regression analyses showed a statistically significant correlation between baseline HbA_{1c} and the symptoms depressed mood, sleeping difficulties, fatigue, appetite problems, feelings of worthlessness and suicidal ideation (Table 2). Although elevated depressive symptoms (PHQ-9 score $\geq$ 10) were related to baseline HbA_{1c} ($\beta = 0.12$, $P = 0.003$), some of the individual symptoms showed a stronger association (e.g. sleeping difficulties and appetite problems). After adjustment for several potential demographic, lifestyle and clinical confounders, the following symptoms remained significantly related to higher baseline HbA_{1c} levels (Table 2): depressed mood, sleeping difficulties, appetite problems and suicidal ideation. Reporting elevated depressive symptoms (PHQ-9 score $\geq$ 10) was also positively associated with HbA_{1c} ($\beta = 0.10$, $P = 0.009$), but more weakly than some of the individual symptoms (e.g. sleeping difficulties and appetite problems). For those with Type 1 diabetes, the symptoms depressed mood, sleeping difficulties, appetite problems, concentration problems, and suicidal ideation were related to higher baseline HbA_{1c} levels, whereas for Type 2 diabetes a significant association with baseline HbA_{1c} was observed for sleeping difficulties, appetite problems and suicidal ideation (Table 2).

Longitudinal analyses

Table 3 shows the relationship between each baseline depressive symptom and the follow-up values of HbA_{1c}. Multivariable analyses showed that depressed mood, sleeping difficulties, appetite problems and psychomotor agitation/retardation were significantly correlated with HbA_{1c} levels after 1 year. For participants with Type 1 diabetes, the symptoms sleeping difficulties, appetite problems, concentration problems and psychomotor changes were related to higher follow-up HbA_{1c} levels, whereas for Type 2 diabetes none of the symptoms were significantly related to follow-up HbA_{1c} levels. Furthermore, none of the depressed symptoms were related to change in HbA_{1c} from baseline to 1-year follow-up in the total sample, except for the symptom suicidal ideation ($\beta = 0.12$, $P = 0.005$, fully adjusted analyses). Patients expressing suicidal ideation at baseline showed a decline in HbA_{1c} over time compared with those without this symptom.

Discussion

In a large cohort of outpatients with diabetes from three tertiary diabetes clinics, we observed that the presence of several individual depressive symptoms (i.e. depressed mood, sleeping problems, appetite problems and suicidal ideation) was associated with higher concurrent HbA_{1c} levels. The baseline depressive symptoms depressed mood, sleeping difficulties, and appetite problems were related to higher HbA_{1c} levels 1 year later. The reported associations were more pronounced in people with Type 1 diabetes. Baseline PHQ-9 symptoms, however, did not predict change in HbA_{1c} over time, except for a decline in HbA_{1c} in patients who expressed suicidal ideation at baseline.

A positive association between depression and HbA_{1c} was observed in a meta-analysis more than 10 years ago for both Type 1 and Type 2 diabetes [6], but some recent longitudinal and intervention studies could not confirm this [10–12]. One of the reasons for the inconsistent results regarding the relationship between depression and HbA_{1c} might be ascribed to the definition of the construct depression. In many studies, depression is treated as a homogeneous syndrome rather than a heterogeneous condition. In analogy with initiatives in psychiatry and psychosomatic research on the 'deconstruction of depression' [20,21], it may be important to focus on the differential characteristics of depression, such as different trajectories and symptoms and their relationship with HbA_{1c}. Furthermore, as the adverse association between depressive symptoms and HbA_{1c} is not restricted to elevated depression scores [22], the entire range of depression scores may be of interest.

Table 1 Baseline characteristics of the sample (n = 646)

	Total		Type 1 diabetes		Type 2 diabetes	
	n	%	*n*	%	*n*	%
Female	329/646	49	158/277	57	170/365	47
Having a partner	483/646	75	214/277	77	265/365	73
Low education (primary school to lower vocational)	183/646	28	45/277	16	138/365	38
Ethnic minority	66/646	10	8/277	3	58/365	16
Type 1 diabetes	277/642	43	277/277	100	0	0
Type 2 diabetes	365/642	57	0	0	365/365	100
Treatment of diabetes						
Diet	93/644	14	20/277	7	73/363	20
Oral medication	199/644	31	12/277	4	187/363	52
Insulin	586/644	91	277/277	100	305/363	84
Severe hypoglycaemic episodes in the last 12 months	164/646	25	92/277	33	70/365	19
Complications (medical chart)						
Cardiovascular disease	137/582	24	18/247	7	119/335	36
Retinopathy	195/590	33	103/254	41	92/336	27
Nephropathy	126/592	21	38/253	15	88/339	26
Neuropathy	137/587	23	45/250	18	92/337	27
Smoking						
Never	297/640	46	136/274	50	159/362	44
Ex-smoker: quit > 1 year ago	191/640	30	64/274	23	126/362	35
Ex-smoker: quit ≤1 year ago	22/640	3	15/274	6	7/362	2
Current smoker	130/640	20	59/274	22	70/362	19
Alcohol						
No	274/641	43	73/276	26	200/361	55
1–7 glasses/week	214/641	33	115/276	42	96/361	27
8–14 glasses/week	98/641	15	62/276	22	36/361	10
> 14 glasses/week	55/641	9	26/276	10	29/361	7
Depression hospitalization in psychiatric hospital during life	21/643	3	9/277	3	12/362	3
Treated for depression in the past	153/640	24	80/275	29	73/361	20
Prevalence of each depressive symptom						
PHQ 1: Lack of interest	92/646	14	33/277	12	59/365	16
PHQ 2: Depressed mood	54/646	8	22/277	8	32/365	9
PHQ 3: Sleeping difficulties	162/646	25	57/277	21	104/365	28
PHQ 4: Fatigue	174/646	27	65/277	23	108/365	30
PHQ 5: Appetite problems	101/646	16	33/277	12	68/365	19
PHQ 6: Worthlessness	76/646	12	29/277	10	47/365	17
PHQ 7: Concentration problems	107/646	17	33/277	12	73/365	20
PHQ 8: Psychomotor agitation/retardation	62/646	10	21/277	8	41/365	11
PHQ 9: Suicidal ideation	71/646	11	23/277	8	48/365	13
	n	Mean (SD)	*n*	Mean (SD)	*n*	Mean (SD)
Age	640	53.3 (15.1)	273	43.9 (13.7)	363	60.5 (11.8)
Duration of diabetes (years)	546	17.5 (11.7)	253	22.1 (12.8)	293	13.6 (8.9)
Body mass index (kg/m^2)	626	27.9 (6.0)	275	25.4 (4.1)	348	30.0 (6.6)
Systolic blood pressure (mmHg, medical chart)	427	136 (18)	180	132 (16)	247	138 (19)
Diastolic blood pressure (mmHg, medical chart)	427	76 (11)	180	75 (10)	247	76 (11)
HbA_{1c} baseline						
mmol/mol	646	61 (14)	277	62 (14)	365	61 (14)
%	646	7.7	277	7.8 (1.3)	365	7.7 (1.3)
	n	Median (IQR)	*n*	Median (IQR)	*n*	Median (IQR)
CES-D score	638	10 (5–18)	276	8 (4–16)	358	11 (5–20)
PHQ-9 score	646	4 (1–9)	277	3 (1–8)	365	4 (1–9)

CES-D, Centre of Epidemiologic Studies Depression; IQR, interquartile range; PHQ-9, Patient Health Questionnaire nine-item version. Type of diabetes unknown, n = 4.

We are aware of one previous study that investigated depressive symptom profiles more closely in relation to HbA_{1c}. Nefs *et al.* [23] showed that anhedonia (loss of interest or pleasure), but not depressed mood or anxiety, was related to suboptimal glycaemic control (HbA_{1c} values above 53 mmol/mol, 7%) in patients with Type 2 diabetes who

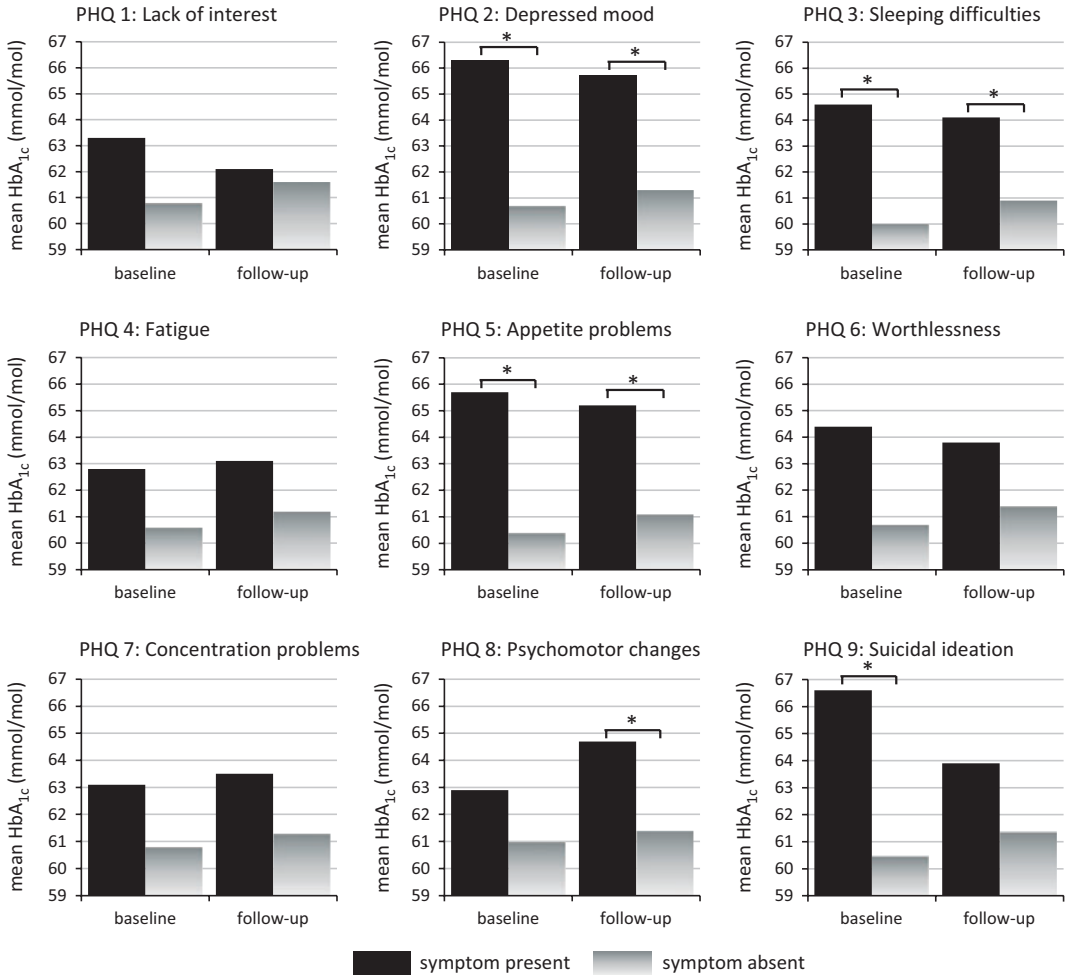

FIGURE 1 Mean HbA_{1c} level in people with (closed bar) and without the symptom (tinted bar), for each of the PHQ-9 symptoms. *$P < 0.05$. To convert HbA_{1c} mmol/mol to%, the following formula can be applied: HbA_{1c} in% = 0.0915 × HbA_{1c} in mmol/mol + 2.15%

were treated in primary care settings, and were generally in good glycaemic control. In contrast, we found no significant association between lack of interest and HbA_{1c} in our sample. Furthermore, we observed a significant association between depressed mood and HbA_{1c} only among people with Type 1 diabetes and not for Type 2 diabetes.

Our study reports standardized beta-values, which enables comparison of the relative importance of associations. All individual symptoms had correlations with elevated HbA_{1c} in the hypothesized direction, although the strength of association for some depressive symptoms was negligible. Moreover, the association of some individual depressive symptoms with HbA_{1c} was more pronounced than that of moderate depression, as indicated by PHQ-9 scores $\geq$ 10.

Overall, we observed that sleeping problems were most strongly related to higher HbA_{1c} values. Sleeping problems are more common in individuals with either Type 1 or Type 2 diabetes compared with those without diabetes [24,25]. Previous studies showed associations of poor glycaemic control with adverse sleep characteristics in individuals with Type 2 diabetes [13,14], but not in individuals with Type 1 diabetes [25]. It remains unclear whether sleeping problems predict or might be a consequence of elevated HbA_{1c} values, or that one or more common denominators causes both sleep problems and poor glycaemic control. For example, sleep problems may also result from frequent nightly urination owing to high glucose levels, or may be caused by obstructive sleep apnoea, which is prevalent among individuals with Type 2 diabetes. However, reduced duration of sleep has been related to impaired glucoregulation and incident diabetes in prospective studies [26], supporting the proposition of sleeping problems influencing glycaemic control in Type 2 diabetes. Sleep disorders are related to alterations of various biological systems (e.g. sympathetic nervous system, hypothalamic–pituitary–adrenal axis, inflammation) which are implicated in glucoregulation [27].

We further observed that appetite problems were related to poor glycaemic control, in particular in participants with Type 1 diabetes. Appetite problems may directly influence

Table 2 Standardized regression coefficients from nine separate linear regression analyses for the association of each Patient Health Questionnaire (PHQ) item and baseline HbA_{1c}

	Model 1		Model 2		Model 3		Model 4	
	β	*P*	β	*P*	β	*P*	β	*P*
Total sample (*n* = 614)								
PHQ 1: Lack of interest	0.07	0.074	0.07	0.104	0.06	0.145	0.05	0.188
PHQ 2: Depressed mood	0.13	0.001	0.12	0.002	0.11	0.004	0.11	0.005
PHQ 3: Sleeping difficulties	0.17	< 0.001	0.17	< 0.001	0.17	< 0.001	0.16	< 0.001
PHQ 4: Fatigue	0.10	0.014	0.08	0.037	0.08	0.040	0.07	0.090
PHQ 5: Appetite problems	0.16	< 0.001	0.15	< 0.001	0.15	< 0.001	0.15	< 0.001
PHQ 6: Worthlessness	0.10	0.015	0.09	0.027	0.08	0.046	0.08	0.05
PHQ 7: Concentration problems	0.07	0.09	0.07	0.070	0.07	0.077	0.07	0.06
PHQ 8: Psychomotor changes	0.04	0.323	0.05	0.257	0.04	0.306	0.04	0.329
PHQ 9: Suicidal ideation	0.16	< 0.001	0.16	< 0.001	0.16	< 0.001	0.14	0.001
Type 1 diabetes (*n* = 268)								
PHQ 1: Lack of interest	0.15	0.017	0.13	0.029	0.13	0.028	0.11	0.054
PHQ 2: Depressed mood	0.17	0.006	0.15	0.010	0.15	0.010	0.15	0.011
PHQ 3: Sleeping difficulties	0.22	< 0.001	0.21	< 0.001	0.22	< 0.001	0.17	0.004
PHQ 4: Fatigue	0.12	0.054	0.09	0.152	0.09	0.148	0.05	0.428
PHQ 5: Appetite problems	0.25	< 0.001	0.24	< 0.001	0.24	< 0.001	0.20	0.001
PHQ 6: Worthlessness	0.13	0.033	0.12	0.049	0.11	0.059	0.08	0.196
PHQ 7: Concentration problems	0.19	0.002	0.19	0.002	0.18	0.002	0.18	0.002
PHQ 8: Psychomotor changes	0.05	0.427	0.04	0.517	0.03	0.586	0.05	0.439
PHQ 9: Suicidal ideation	0.16	0.009	0.16	0.008	0.15	0.011	0.13	0.025
Type 2 diabetes (*n* = 343)								
PHQ 1: Lack of interest	0.03	0.628	0.02	0.694	0.01	0.830	0.01	0.883
PHQ 2: Depressed mood	0.10	0.054	0.10	0.067	0.08	0.127	0.08	0.137
PHQ 3: Sleeping difficulties	0.15	0.006	0.15	0.007	0.14	0.007	0.14	0.010
PHQ 4: Fatigue	0.09	0.079	0.09	0.110	0.08	0.128	0.07	0.223
PHQ 5: Appetite problems	0.11	0.050	0.10	0.073	0.10	0.055	0.11	0.040
PHQ 6: Worthlessness	0.08	0.141	0.07	0.183	0.06	0.273	0.06	0.309
PHQ 7: Concentration problems	0.00	0.985	0.01	0.915	0.01	0.904	0.00	0.927
PHQ 8: Psychomotor changes	0.04	0.464	0.05	0.368	0.05	0.377	0.05	0.370
PHQ 9: Suicidal ideation	0.17	0.002	0.17	0.001	0.16	0.004	0.14	0.008

Model 1, unadjusted; Model 2, adjusted for sex, age; Model 3, adjusted for sex, age, education, ethnic minority; Model 4, adjusted for sex, age, education, ethnic minority, insulin treatment, body mass index, smoking.

HbA_{1c} values and vice versa. Alternatively, appetite problems might be a result of sleep problems. For example, experimental and observational studies show that sleep loss is related to an up-regulation of the appetite-stimulating hormone ghrelin and down-regulation of the satiety hormone leptin in persons without diabetes [28].

We further observed that two cognitive–affective symptoms of depression (depressed mood, and suicidal ideation) were significantly related to HbA_{1c} in the total sample. Depressed mood and suicidal ideation may be indicators for a more severe type of depression. They may be related to HbA_{1c} mainly because of poorer self-care aspects (e.g. taking prescribed medications), although biological changes are also possible. The relationship of suicidal ideation at baseline with a subsequent decline in HbA_{1c} was surprising. Possibly, suicidal ideation is linked to concurrent levels of HbA_{1c} rather than future levels. The severity symptom may have been reduced over time together with HbA_{1c}, although we lacked follow-up data of this symptom to verify this.

Some depressive symptoms (e.g. fatigue, appetite problems) may overlap with symptoms of prolonged hyperglycaemia. McDade *et al*. [29], however, showed that the structure of depression and anxiety symptoms is similar across individuals with diabetes and adults in the general community without diabetes. Although the overlapping symptoms of hyperglycaemia and depression may result from glycaemic disturbances, they showed that these symptoms were, nonetheless, strongly associated with mood and distress, and argued that overlapping symptoms should not immediately be attributed to the diabetes disease process [29].

Because correlations between each symptom and HbA_{1c} were small, the symptoms will explain only a small part of the variance in HbA_{1c}. However, the mean difference in HbA_{1c} between patients with and patients without individual depressive symptoms was up to 6 mmol/mol (0.5%), which is considered a clinically relevant difference.

Strengths of the current study are the large sample size, the use of longitudinal data for HbA_{1c}, and the inclusion of a mixed sample of people with Type 1 and Type 2 diabetes. Furthermore, we used the items of PHQ-9, which corresponds to the DSM-IV symptoms of major depression. However, limitations of the study should also be acknowledged. First, the PHQ-9 was validated for the construct depression but not for the constructs of each single symptom of depression. Second, the use of the PHQ-9 limited our conclusions regarding the direction of the association as

Table 3 Standardized regression coefficients from nine separate linear regression analyses for the association of each Patient Health Questionnaire (PHQ) item and follow-up HbA_{1c}

	Model 1		Model 2		Model 3		Model 4	
	β	*P*	β	*P*	β	*P*	β	*P*
Total sample (*n* = 525)								
PHQ 1: Lack of interest	0.02	0.595	0.02	0.656	0.02	0.710	0.02	0.721
PHQ 2: Depressed mood	0.11	0.013	0.10	0.021	0.10	0.026	0.09	0.031
PHQ 3: Sleeping difficulties	0.13	0.003	0.13	0.003	0.13	0.003	0.12	0.004
PHQ 4: Fatigue	0.09	0.039	0.07	0.100	0.07	0.099	0.06	0.136
PHQ 5: Appetite problems	0.12	0.004	0.11	0.009	0.11	0.008	0.11	0.011
PHQ 6: Worthlessness	0.07	0.112	0.06	0.152	0.06	0.181	0.06	0.150
PHQ 7: Concentration problems	0.06	0.139	0.07	0.099	0.07	0.094	0.08	0.066
PHQ 8: Psychomotor changes	0.08	0.069	0.09	0.043	0.09	0.039	0.09	0.038
PHQ 9: Suicidal ideation	0.08	0.085	0.08	0.065	0.08	0.081	0.07	0.100
Type 1 diabetes (*n* = 232)								
PHQ 1: Lack of interest	0.15	0.022	0.13	0.039	0.13	0.041	0.12	0.053
PHQ 2: Depressed mood	0.13	0.043	0.12	0.064	0.12	0.065	0.12	0.056
PHQ 3: Sleeping difficulties	0.24	< 0.001	0.23	< 0.001	0.23	< 0.001	0.21	0.001
PHQ 4: Fatigue	0.13	0.046	0.10	0.144	0.10	0.142	0.08	0.217
PHQ 5: Appetite problems	0.20	0.002	0.19	0.003	0.20	0.003	0.17	0.010
PHQ 6: Worthlessness	0.07	0.294	0.06	0.350	0.06	0.336	0.05	0.428
PHQ 7: Concentration problems	0.18	0.005	0.18	0.004	0.18	0.004	0.19	0.003
PHQ 8: Psychomotor changes	0.12	0.061	0.12	0.066	0.12	0.059	0.13	0.038
PHQ 9: Suicidal ideation	0.04	0.536	0.03	0.649	0.03	0.626	0.03	0.605
Type 2 diabetes (*n* = 291)								
PHQ 1: Lack of interest	–0.06	0.287	–0.06	0.286	–0.07	0.242	–0.07	0.269
PHQ 2: Depressed mood	0.09	0.138	0.08	0.160	0.07	0.213	0.07	0.250
PHQ 3: Sleeping difficulties	0.05	0.354	0.05	0.358	0.05	0.376	0.05	0.361
PHQ 4: Fatigue	0.07	0.237	0.06	0.322	0.05	0.352	0.05	0.412
PHQ 5: Appetite problems	0.07	0.208	0.06	0.294	0.06	0.278	0.07	0.248
PHQ 6: Worthlessness	0.07	0.200	0.07	0.261	0.06	0.317	0.07	0.272
PHQ 7: Concentration problems	0.00	0.964	0.01	0.902	0.01	0.871	0.02	0.769
PHQ 8: Psychomotor changes	0.06	0.349	0.07	0.264	0.07	0.232	0.07	0.221
PHQ 9: Suicidal ideation	0.10	0.077	0.11	0.055	0.11	0.075	0.10	0.094

Model 1, unadjusted; Model 2: adjusted for sex, age; Model 3, adjusted for sex, age, education, ethnic minority; Model 4, adjusted for sex, age, education, ethnic minority, insulin treatment, body mass index, smoking.

some of its items were double-barrelled. For example, the item 'appetite problems' in PHQ-9 describes both increased and decreased appetite. Similarly, the item on sleeping difficulties describes both insomnia and excessive sleeping. Third, depressive symptoms were only assessed at baseline and not at follow-up, which limits the results of longitudinal analyses. Fourth, it remains possible that the selection of patients with diabetes from tertiary diabetes clinics only, and the low uptake of the postal questionnaire, have biased the associations for diabetes patients in general. Finally, our study had an explorative character, in particular the analyses stratified for Type 1 and Type 2 diabetes, which limits more definitive statements regarding the association between depressive symptoms and HbA_{1c}.

Patients with elevated HbA_{1c} values are to be considered an at-risk group for specific depressive symptoms and therefore warrant special attention. HbA_{1c} is a potential clinical mediator of the relationship between depressive symptoms and diabetes complications [30]. Future prospective studies should be conducted to confirm this proposed mediation, taking into account the heterogeneous phenomenology of depression.

In summary, the heterogeneity of depression may help to explain why some studies found relationships between depression and HbA_{1c} while others did not, as some symptoms may link more strongly to HbA_{1c}. We found that depressed mood, sleeping difficulties, appetite problems and suicidal ideation appear to be more strongly related to HbA_{1c} levels, in particular in individuals with Type 1 diabetes.

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Competing interests

Nothing to declare

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